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# α-Ketenyl Radical Intermediates in the Synthesis of Propellanes. A Formal Synthesis of Modhephene

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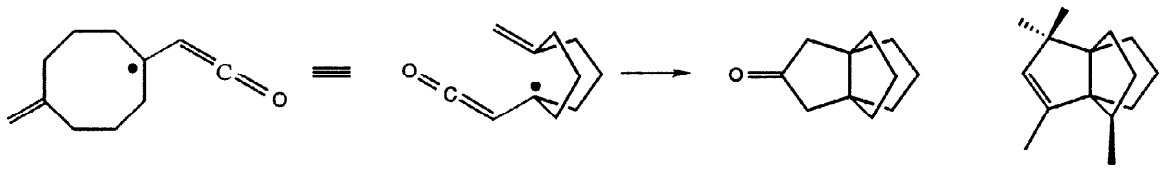
***Abstract:*** A tandem transannulation – cyclisation sequence from a cyclooctenyl substituted α-ketenyl radical intermediate, *viz* **1**, is used as the basis of a new, formal, synthesis of the naturally occurring triquinane modhephene **2**.


α-Ketenyl radicals, RC•HC=C=O, are novel reactive intermediates which can be produced cleanly and efficiently when α, β-unsaturated selenyl esters are treated with $Bu_3SnH$ – AIBN.[1] In earlier work we have demonstrated that these reactive intermediates participate in intramolecular ring forming reactions where they are terminated by radical *exo* dig processes into the sp-carbon centre of the ketene electrophore.[2] In an extension to these studies we now describe a concise approach to 3,3,3-propellanes and a formal synthesis of (±)-modhephene **2** involving the tandem transannulation – cyclisation sequence from the cyclooctenyl substituted α-ketenyl radical intermediate **1** shown in **Scheme 1.**



**1** **2**

**Scheme 1**

Thus we first synthesised the carboxylic acid precursor **5** to the α-ketenyl radical **1** starting from the known 5-methylenecyclooctanone **3**[3] following Peterson olefination, to **4**, and saponification. Treatment of the carboxylic acid **5** with *N*-phenylselenylphthalimide – $PPh_3$ failed to produce any of the corresponding selenyl ester[1,2] and instead we prepared the 2-(*o*-iodophenyl) ethyl thioester **6**[4] as an alternative precursor to **7**. When this ester **6** was treated with $Bu_3SnH$-AIBN in refluxing benzene it underwent smooth transannulation – cyclisation in the anticipated sense and produced the known tricyclo [3.3.3.0.$^{1,5}$] undecan-3-one **10**[5] in 56%

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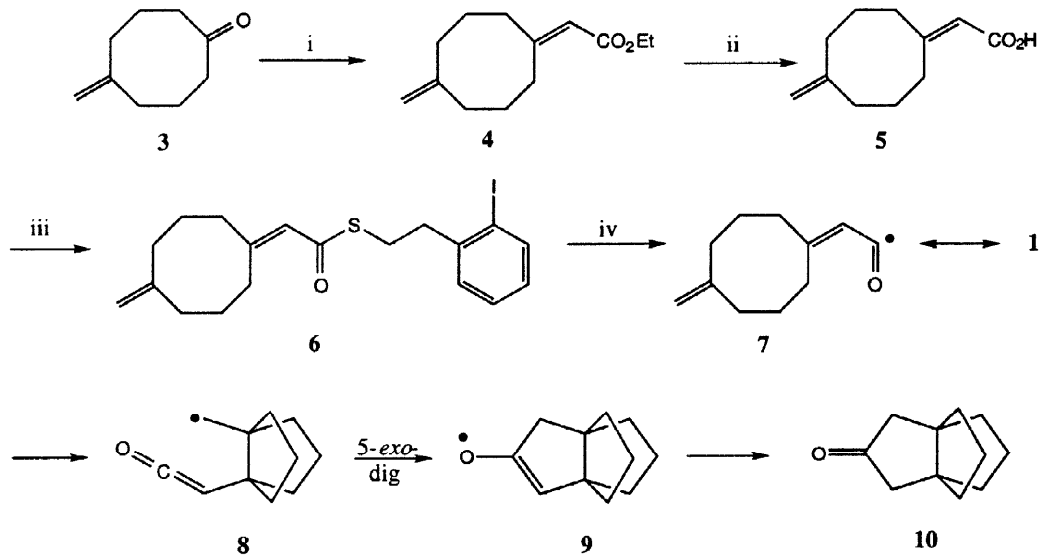
yield. The propellane **10** is produced from the thioester **6** following formation of the α,β-unsaturated acyl radical intermediate **7** which takes part in a 5-*exo* trig transannulation *via* its α-ketenyl radical counterpart **1**, leading to **8**; the radical **8** then undergoes intramolecular 5-*exo* dig cyclisation into the ketene electrophore giving rise to **9**.



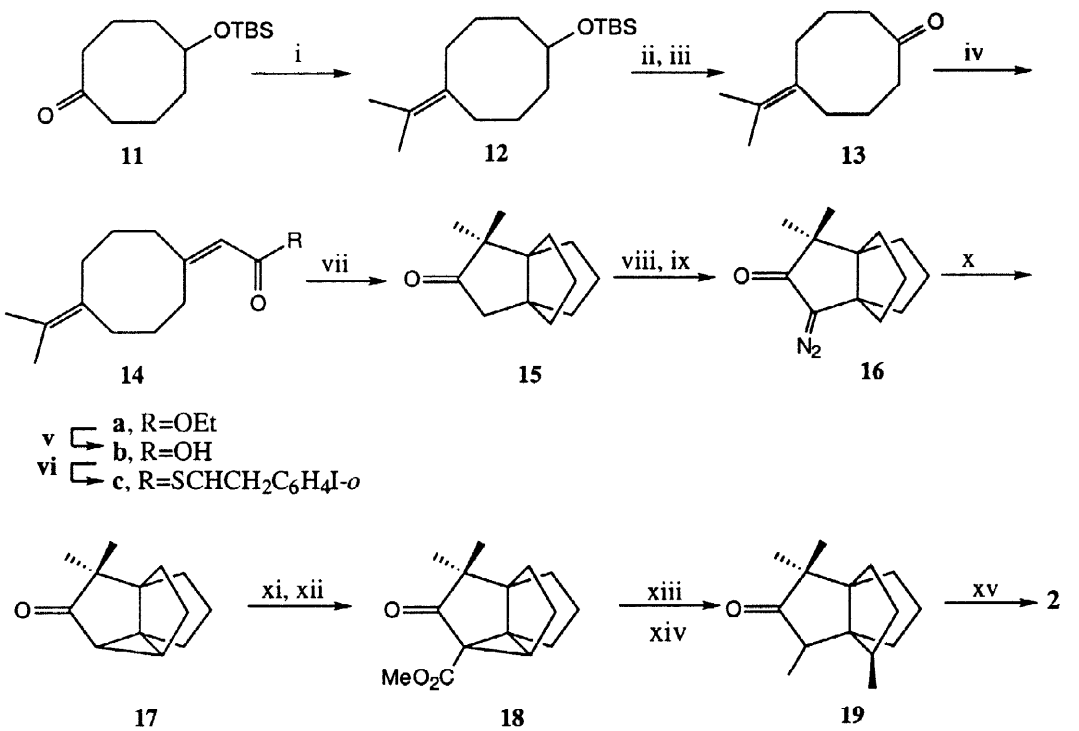

*Reagents: i*, $TMSCH_2CO_2Et$, LDA, THF, -78°C, 54%; *ii*, 1M NaOH, $H_2O$, Δ, 96%; *iii*, 2-(o-$IC_6H_6$)$CH_2CH_2SH$, DCC, DMAP, $CH_2Cl_2$, 72%; *iv*, $Bu_3SnH$, AIBN, benzene, Δ, 56%.

**Scheme 2**

We next synthesised the *gem*-dimethyl substituted derivative **14c**, corresponding to **6** based on an initial intermolecular McMurry coupling reaction between the cyclooctanone **11** and acetone in the presence of $3AlCl_3{\cdot}TiCl_3$ and Li metal[6] which led to **12**. Hydrolysis of the silyl group protection in **12**, followed by oxidation of the resulting alcohol next produced the cyclooctanone **13**. A Peterson olefination between **13** and ethyl trimethylsilylacetate in the presence of LDA at -78°C gave rise to the unsaturated ester **14a** which was saponified to the carboxylic acid **14b** using 1M aqueous NaOH. Finally, treatment of the acid **14b** with 2-(2-iodophenyl) ethanethiol in the presence of DMAP gave the thioester **14c**. When the thioester **14c** was treated with $Bu_3SnH$-AIBN in hot benzene for 5h, work-up and chromatography produced the tricyclic ketone **15** in 60% yield. The tricyclic ketone **15** was next converted into its corresponding α-diazo derivative **16** which on heating in toluene in the presence of $CuSO_4$ was elaborated to the tetracyclo [3.3.3.0.$^{1,5}$0$^{2,8}$] undecane-3-one **17**. The tetracycle **17** has been used by Cook *et al* [7] in a synthesis of (±)-modhephene following: i) conversion into

the ester **18**, ii) lithium dimethylcuprate Michael addition, methylation and demethoxycarbonylation to **19**: and finally iii) reduction and dehydration (Scheme 3).

Our concise synthesis of the tricyclic ketone **15** involving tandem transannulation-cyclisation from the α-ketenyl radical intermediate derived from **14b** thus constitutes a formal synthesis of natural modhephene **2**.[8,9] Further studies are in progress to develop the scope for α-ketenyl radicals in alternative ring constructions.




*Reagents*: *i*, $3TiCl_3.AlCl_3$, Li, $Me_2CO$, Δ, 52%; *ii*, 40% HF, $H_2O$-$CH_3CN$, 48%; *iii*, $(COCl)_2$, DMSO, $CH_2Cl_2$, -60°C, 69%; *iv*, $Me_3SiCH_2CO_2Et$, LDA, THF, -78°C, 65%; *v*, 1M NaOH, $H_2O$, Δ, 55%; *vi*, 2-(o-$IC_6H_4$)$CH_2CH_2SH$, DCC, DMAP, $CH_2Cl_2$ 85%; *vii*, $Bu_3SnH$-AIBN, benzene, Δ, 59%; *viii*, NaH, MeOCHO; *ix*, $TsN_3$,$Et_2NH$; *x*, $CuSO_4$, toluene, Δ; *xi*, $^tBuLi$, $CO_2$; *xii*, HCl, $CH_2N_2$; *xiii*, $Me_2CuLi$; *xiv*, MeI, $KOBu^t$, then LiI, collidine, Δ; *xv*, $LiAlH_4$, then $H_2O$.

**Scheme 3**

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